第69回生命科学先端研究センター
学術セミナー

日時：平成23年３月10日（木）午後３時～４時

場所：杉谷キャンパス 共同利用研究棟６階 会議室

講師：Claus Scheidereit 教授
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演題：「How genotoxic stress activates transcription factor NF-κB: A tale of poly (ADP-ribose)- and ubiquitin-scaffolds」

ABSTRACT: The IKK/NF-κB system is a prototypic signaling cascade with widespread medical importance. It regulates important processes in normal physiology and in the diseased state, including lymphocyte differentiation, embryonic epidermal development, chronic inflammation and tumor formation. NF-κB is also linked in complex regulatory networks to the DNA damage response. As a potent anti-apoptotic regulator, NF-κB acts to limit genotoxic stress-induced cell death and counteracts the activity of p53. Thus, NF-κB activation may impair the efficiency of genotoxic cancer therapy.

It has been an intriguing problem, how the nuclear DNA damage signal is transmitted to the cytoplasm to trigger NF-κB activation. Signal transmission is shown to be achieved through an ordered network of various posttranslational modifications. The SUMO1 ligase PIASγ and the kinase *ataxia talengiectasia mutated* (ATM) have been implicated to consecutively SUMOylate and phosphorylate nuclear IKKγ (NEMO, the regulatory IκB kinase subunit), which in turn results in activation of cytoplasmic IKK holocomplexes. Through proteomic analyses of IKK-associating components and use of knockout cells, poly (ADP-ribose)-polymerase-1 (PARP-1) could be identified as the DNA proximal regulator, which senses DNA strand breaks. Through poly(ADP-ribose) (PAR) synthesis, PARP-1 forms a scaffold to assemble IKKγ, PIASγ and ATM in a dynamic and transient manner. Nuclear signalosome formation involves direct binding of ATM and PIASγ to ADP-ribose polymers through PAR binding motifs. PAR binding of PIASγ is required for IKKγ SUMOylation. Subsequently, activated ATM and SUMOylated IKKγ are exported to the cytoplasm to activate enzymatic IKK holocomplexes. ATM binds to TRAF6 to induce lysine63-linked polyUb synthesis. TRAF6 ubiquitination then activates TAK1 and triggers cIAP1-dependent IKKγ monoubiquitination. However, IKKγ monoubiquitination depends not only on ATM, but also on PARP-1 and prior SUMOylation of IKKγ and it is essential for IKK and NF-κB activation. Thus, DNA double strand breaks trigger a complex, spatially ordered interplay of kinases, ubiquitin- and SUMO-ligases and PAR polymerase to activate NF-κB. The implications of these findings for tumor therapy will be discussed.

Reference: 1) Hinz M, Stilmann M, Arslan SÇ, Khanna KK, Dittmar G, Scheidereit C. Mol Cell. 40, 63-74, 2010. 2) Stilmann M, Hinz M, Arslan SC, Zimmer A, Schreiber V, Scheidereit C. Mol Cell. 36, 365-378, 2009.

※Scheidereit教授は炎症シグナルと転写制御研究の第一人者で、2005年にはドイツ医学の最高権威のドイツ癌賞を授与されました。この度、本学テニュアトラック・キックオフ・ミーティングの基調講演のため来日されました。エキサイティングな最近の研究の講演を聴くことができると思います。大変良い機会ですので、皆様のご来聴をよろしくお願い申し上げます。

◎問い合わせ先
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